Remarks

The Office Action mailed August 15, 2003 has been received and reviewed. The pending claims are claims 1-17. Reconsideration and withdrawal of the rejections are respectfully requested.

Traverse of the Restriction Requirement

Applicants continue to traverse the Restriction Requirement (mailed July 17, 2002), submitting that claims 1-6, 9-11, 14 and 15 are linking claims. Applicants acknowledge with appreciation the Examiner's statements "that claims 1-6, 9-11, 14 and 15 may be linking claims," and "that upon reaching allowable matter, rejoinder of groups will be considered" (¶5, pages 2-3 of Office Action mailed August 15, 2003). Applicants request rejoinder upon the identification of allowable matter.

The Objection to the Claims

The Examiner objected to claims 1-17 for the recitation of the non-elected inventions SEQ ID NO's 2-34. In view of the Applicants' request for the rejoinder of SEQ ID NO:2-34, discussed above, Applicants respectfully submit that this objection be held in abeyance pending the identification of allowable subject matter.

The 35 U.S.C. §112, First Paragraph, Rejection

The Examiner rejected claims 1-17 under 35 U.S.C. §112, first paragraph, because the specification does not reasonably provide enablement for the claimed methods. Applicants disagree and respectfully traverse this rejection. Applicants submit that the specification provides adequate teaching and guidance for the claimed methods.

Further, with an enablement rejection, "the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, USPQ2d 1510, 1513 (Fed, Cir. 1993). And, "it is incumbent upon

the Patent Office . . . to back up assertions of its own with acceptable evidence or reasoning." *In re Marzocchi* 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). "This can be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact. . . . However, specific technical reasons are always required. *In re Marzocchi* 439 F.2d at 224, 169 USPQ at 370 (see also, MPEP 2164.04).

As discussed in more detail below, Applicants respectfully submit that the Patent Office has failed to meet this burden, has failed to back up its assertions with acceptable evidence or reasoning. Reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is respectfully requested.

The Rejection of Claims 1-8 and 16

The Examiner rejected claims 1-8 and 16 under 35 U.S.C. §112, first paragraph, "because the specification, while being enabling for promoting neuronal cell differentiation *in vitro* with SEQ ID NO.: 2, full-length colostrinin, or active analogs, does not reasonably provide enablement for the claimed methods for promoting neuronal differentiation *in vivo*" (page 3, ¶8, Office Action mailed August 15, 2003). Applicants disagree and respectfully traverse this rejection of claims 1-8 and 16.

In paragraph 10, page 4, of the Office Action mailed August 15, 2003, while acknowledging that the "PC12 and SH-SHY5Y cell lines are well characterized and well accepted *in vitro* model systems for the study of neuronal differentiation," the Examiner asserted that the PC12 and SH-SHY5Y cell lines are not predictive of successful results *in vivo*. Applicants adamantly disagree. As previously presented, Applicants submit that the correlation between the *in vitro* model systems provided by the PC12 and SH-SY5Y cells lines and *in vivo* results is well accepted. In support of this statement, Applicants again provide the following representative sampling of the scientific literature, supporting the correlation between *in vitro* results with the SH-SY57 and PC12 cells lines and *in vivo* results:

Noble et al., *Molecular Pharmacology*, 2000;58:159-166; Demonstrating the similarity of the stimulation of μ- or δ-opioid receptors both *in vitro* in the SH-SY57 cell line and *in vivo* in different strains of mice and rats.

DeJongh et al., *Toxicology and Applied Pharmacology*, 1999; 158:261-268; Demonstrating acrylamide toxicity both *in vitro* in the SH-SY5Y cell line and *in vivo* in rats.

Chen et al., *Journal of Neurochemistry*, 1998;70(4): 1768-1771; Demonstrating the induction of tyrosine hydroxylase by lithium both *in vitro* in the SH-SY5Y cell line and *in vivo* in the frontal cortex, hippocampus, and striatum of male Wistar rats.

Ponthan et al., *Int. J. Cancer*, 2003;104: 418-424; Demonstrating toxicity and antiproliferative effects of the synthetic retinoid Ro 13-6307 both *in vitro* in SH-SY5Y cells and *in vivo*, in a rat neuroblastoma xenograft model.

Zhen et al., *Psychopharmacology*, 2002;162: 379-384; Demonstrating the stimulation of protein tyrosine phosphatase (PTPase) by lithium both *in vitro* in the PC12 cell line and *in vivo* in rat brains.

Dago et al., *Journal of Neurochemistry*, 2002;81: 17-24; Demonstrating the correlation of the neuroprotective effect of compound NS1231 *in vitro* in PC12 cells with the neuroprotective effect of compound NS1231 *in vivo* in both a gerbil model of transient global ischaemia and a mouse middle cerebral artery occlusion model.

Bagchi et al., *Toxicology Letters*, 1997;91: 31-37; Demonstrating similar protein kinase C (PKC) stimulatory effects *in vitro*, with the PC12 cell line, and *in vivo*, with Sprague-Dawley rats, by the administration of various pesticides and transition metal salts, all known to induce oxidative stress.

In paragraph 11, page 4, of the Office Action mailed August 15, 2003, the Examiner asserted that the "specification fails to provide any guidance for the successful use of SEQ ID NO:2 and its functional analogues." This is incorrect. Page 11, line 20, through page 14, line 14, of the specification provide guidance for the preparation and administration of colostrinin, constituent peptides thereof, including SEQ ID NO:2, and active analogs thereof.

The Examiner continued with the assertion that "since resolution of the various complications in regards to targeting the effect of the protein in an organism in neuronal cell differentiation is highly unpredictable, one of skill in the art would have been unable to practice that invention without engaging in undue trial and error experimentation." Applicants respectfully submit that this statement is the unsubstantiated opinion of the Examiner. The Examiner is invited to identify the "various complications" he has made reference to, and it is requested that he provide appropriate evidence to substantiate this opinion.

Finally, Applicants are confused by the Examiners assertion in paragraph 11, that "[i]n order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require *de novo* determination of formulations with known neuronal cell differentiation signs and symptoms to correlate with SEQ ID NO:2 administration." Applicants request clarification of this statement. And, as presented above, Applicants submit that the specification provides adequate guidance for the preparation and administration of colostrinin, constituent peptides thereof, including SEQ ID NO:2, and active analogs thereof.

In paragraph 12, page 5, of the Office Action mailed August 15, 2003, the Examiner asserted that the specification "does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of using SEQ ID NO:2 . . . in a patient," and that "a person skilled in the art would recognize that predicting the efficacy of using a specific polypeptide . . . *in vivo* based solely on its performance *in vitro* is highly problematic." Thus, "although the specification prophetically considers and discloses general methods of using the claimed methods" *in vivo*, such a "disclosure would not be considered enabling since the state of neuronal cell differentiation is highly unpredictable." Applicants adamantly disagree. Applicants submit that the Examiner's statement that "a person skilled in the art would recognize that predicting the efficacy of using a specific polypeptide . . . *in vivo* based solely on its performance *in vitro* is highly problematic" is an overly broad generalization. Applicants submit

that the Examiner's statement that "the state of neuronal cell differentiation is highly unpredictable" is unsubstantiated opinion on the part of the Examiner.

Finally, by acknowledging that the "specification prophetically considers and discloses general methods of using the claimed methods" *in vivo*, but concluding that the specification "does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of using SEQ ID NO:2 ... ***in a patient***" (emphasis added), the Examiner is inappropriately requiring the Applicant to present data from *in vivo* animal experiments or from human clinical trials.

In paragraph 13, pages 5-6, of the Office Action mailed August 15, 2003, the Examiner summarized the introductory section of Popik et al., (*Behavioral Brain Research* 118(2):201-208, 2001), as teaching that colostrinin "induces maturation and differentiation of murine thymocytes and affects humoral and cellular immune reactions in both *in vitro* cultures and *in vivo*." Applicants respectfully submit that the correlating *in vitro* and *in vivo* results shown by Popik et al. with colostrinin directly refute the Examiner's earlier broad generalization, that "a person skilled in the art would recognize that predicting the efficacy of using a specific polypeptide . . . *in vivo* based solely on its performance *in vitro* is highly problematic" (paragraph 12, page 5, Office Action, mailed August 15, 2003).

In paragraph 14, page 6, of the Office Action mailed August 15, 2003, referring to the experimental teachings of Popik et al., the Examiner concluded that "[t]aking Popik et al. into account, a skilled artisan would have doubt that colostrinin analogs were . . . acting as *'neuronal cell regulators' in vivo*" (emphasis in original). Applicants respectfully submit that this conclusion is not based on sound scientific reasoning and is invalid. Popik et al. administered the colostrinin-derived nonapeptide CVNP *in vivo* to aged rats and measured cognitive effects using such behavioral procedures as having the rats swim in a water maze (the "Morris water maze") and move about in an automatic shuttle-box apparatus (the "Active avoidance test") (see Popik et al., "Materials and Methods," pages 202-203). It appears that the Examiner is incorrectly equating these various behavioral observations with the claimed methods

of "promoting cell differentiation . . . comprising contacting cells with a neuronal cell regulator . . . under conditions effective to change the cells in morphology to form neuronal cells" (claims 1-8) and "promoting neuronal cell differentiation . . . comprising contacting pluripotent cells of the nervous system with a neuronal cell regulator . . . under conditions effective to change the pluripotent cells of the nervous system in morphology to form neuronal cells" (claim 16). Furthermore, Applicants note that the Examiner's statement that "Popik et al. attribute the effects of CVNP on the rats to their immunomodulatory properties and not any direct effect on the nervous system" is incorrect, taking the concluding statements of Popik et al. out of context. In more complete context Popik et al. states "[a]t present we are unable to propose the mechanism of action of CVNP. It cannot be excluded that its immunomodulatory effects may be of importance. . . . However, whether or not the immunomodulatory effects of colostrinin-derived nonapeptide are of importance for the improvement of cognitive functions in rats, remains to be established" (Popik et al., last complete paragraph on page 207).

In paragraph 15, page 6, of the Office Action mailed August 15, 2003, the Examiner cited Inglot et al. (*Arch Immunol. Ther. Exp* 44(4):215-224, 1996) as teaching "that colostrinin or an active analog thereof . . . induces IFN and TNF-α production in human peripheral blood monocytes (PBL) *in vitro*." From these teachings, the Examiner concluded that "[i]n light of this evidence, a person of ordinary skill in the art would doubt that these colostrinin analogs were inducing (*sic*) acting as 'neuronal cell regulators' and changing 'the cells in morphology to form neuronal cells.'"Applicants adamantly disagree and insist that the Examiner substantiate this statement with credible evidence and/or reasoned scientific arguments.

Applicants submit that the induction of IFN and TNF-α by colostrinin and colostrinin analogs has no relevance to the claimed methods promoting cell differentiation under conditions effective to change the cells in morphology to form neuronal cells. Further, it appears as if the Examiner has chosen to discredit the actual showings of the Applicants' specification. Applicants submit that the Example section (pages 14-19 of the specification) shows the change

in cell morphology to form neuronal cells that the Examiner asserted Inglot et al. leads one of ordinary skill in the art to doubt could occur.

In view of the arguments presented above, Applicants respectfully submit that the specification provides adequate instruction and guidance for the methods of claims 1-8 and 16, for methods of *in vivo* administration. Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph.

The Rejection of Claims 9-13

The Examiner rejected claims 9-13 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection of claims 9-13.

In paragraph 20, page 7, of the Office Action mailed August 15, 2003, the Examiner asserted that "while PC12 and SH-SHSY5Y cells are an art-accepted *in vitro* model to study cell differentiation, they are not indicative of the unpredictability and obstacles to practicing the invention in vivo." Applicants respectfully submit that this statement is the unsubstantiated opinion of the Examiner. The Examiner is invited to provide the appropriate evidence to substantiate this opinion.

The Examiner further asserted "that the Applicant has not provided any examples of *in vivo* use of SEQ ID NO:2;" and that the "specification as filed only offers a prophetic example . . . rather than work actually conducted." Applicants disagree and refer the Examiner to the responses to these same arguments presented earlier in this communication.

In paragraph 21, page 8, of the Office Action mailed August 15, 2003, the Examiner again cited Popik et al. as teaching the immunomodulatory effects of colostrinin, and concluded that Popik et al. is a working example of the immunomodulatory effects of colostrinin. From this the Examiner concluded the administration of "colostrinin and its functional analogues *in vivo* do not show any neuronal differentiation *in vivo*." Applicants

submit that, apart from providing evidence that the level of skill in the arts of colostrinin formulation and the general administration of colostrinin to patients are quite highly developed, Popik et al. is silent as to any neuronal differentiation. Applicants submit that the administration of a product in one method, under conditions effective to accomplish one result (immunomodulation) has little relevance to the administration of a similar product in a second, different method under different effective conditions, conditions effective to accomplish a second, different result. Applicants do not understand the logic of the Examiner's argument.

In paragraph 22, page 8, of the Office Action mailed August 15, 2003, the Examiner asserted that none of the various references cited by the Applicant in the previous response "are concerned with the representative of either [the PC12 or the SH-SHSY5Y] cell line for therapeutic applications." This is incorrect. Many of the previously cited references directly support the therapeutic applications of the PC12 and the SH-SHSY5Y cell lines. For example, see:

Noble et al., *Molecular Pharmacology*, 2000;58:159-166; Demonstrating the similarity of the stimulation of μ- or δ-opioid receptors both *in vitro* in the SH-SY57 cell line and *in vivo* in different strains of mice and rats.

Chen et al., *Journal of Neurochemistry*, 1998;70(4): 1768-1771; Demonstrating the induction of tyrosine hydroxylase by lithium both *in vitro* in the SH-SY5Y cell line and *in vivo* in the frontal cortex, hippocampus, and striatum of male Wistar rats.

Ponthan et al., *Int. J. Cancer*, 2003;104: 418-424; Demonstrating toxicity and antiproliferative effects of the synthetic retinoid Ro 13-6307 both *in vitro* in SH-SY5Y cells and *in vivo*, in a rat neuroblastoma xenograft model.

Zhen et al., *Psychopharmacology*, 2002;162: 379-384; Demonstrating the stimulation of protein tyrosine phosphatase (PTPase) by lithium both *in vitro* in the PC12 cell line and *in vivo* in rat brains.

Dago et al., *Journal of Neurochemistry*, 2002;81: 17-24; Demonstrating the correlation of the neuroprotective effect of compound NS1231 *in vitro* in PC12 cells with the

neuroprotective effect of compound NS1231 *in vivo* in both a gerbil model of transient global ischaemia and a mouse middle cerebral artery occlusion model.

In view of the arguments presented above, Applicants respectfully submit that the specification provides adequate instruction and guidance for the methods of claims 9-13, for promoting neuronal cell differentiation in a patient. Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph.

The Rejection of Claims 14, 15, and 17

The Examiner rejected claims 14, 15, and 17 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection of claims 14, 15, and 17.

In paragraphs 26-27, page 9, of the Office Action mailed August 15, 2003, the Examiner cited the teachings of WO 98/14773, on the immunomodulatory effects of colostrinin. In paragraph 30, page 10, of this Office Action, the Examiner cited that teachings of Kruzel et al., demonstrating the ability of colostrinin constituent peptides to induce cytokines and reduce oxidative stress. In paragraph 31, page 10 of this Office Action, the Examiner cited the teachings of Zimecki et al., demonstrating the effect of the proline-rich polypeptide PRP for the treatment of immune cell nonfunction. Applicants do not understand the relevance of these teachings to the instant invention.

In paragraph 28, page 9, of the Office Action mailed August 15, 2003, the Examiner asserted that "it remains to be shown in the art or through the instant Specification that colostrinin, its constituent peptides, and analogs thereof have activity as neuronal regulators." Applicants respectfully disagree and submit that the specification adequately demonstrates the

neuronal regulatory effect of colostrinin, constituent peptides thereof, active analogs thereof, and combinations thereof.

In paragraph 29, pages 9-10, of the Office Action mailed August 15, 2003, the Examiner asserted that "the claims as written read on the use of SEQ ID NO:2 and its functional analogues to revive dead tissue, resurrect deceased patients who have died from brain failure, and repair all known and unknown causes of nonfunctional neurons. This is clearly not supported by the Specification and prior art." Applicants submit that the Examiner's statement is inappropriate exaggeration.

Claim 14 is drawn to a "method for treating damaged neuronal cells. . . comprising contacting nonfunctional neuronal cells with a neuronal cell regulator . . . under conditions effective to convert the damaged neuronal cells to functional neuronal cells . . . wherein the nonfunction is the result of neurodegeneration." Claim 15 is drawn to a "method for treating damaged neuronal cells in a patient . . . comprising administering to the patient a neuronal cell regulator . . . under conditions effective to convert damaged neuronal cells to functional neuronal cells . . . wherein the nonfunction is the result of neurodegeneration." And, claim 17 is drawn to a "method for promoting neuronal cell differentiation in a patient . . . comprising administering to the patient a neuronal cell regulator . . . under conditions effective to promote differentiation of pluripotent cells of the nervous system to form neuronal cells."

In paragraph 32, page 10, of the Office Action mailed August 15, 2003, the Examiner asserted that "the *in vitro* system as presented in the instant application is not predictive of an *in vivo* method." Applicants respectfully submit that this statement is the unsubstantiated opinion of the Examiner. The Examiner is requested to provide the appropriate evidence to substantiate this opinion.

Applicants respectfully submit that the specification provides adequate instruction and guidance for the methods of claims 14, 15, and 17. In view of the arguments presented above, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph.

Summary

It is respectfully submitted that the pending claims 1-17 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
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CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that the Transmittal Letter and the paper(s), as described hereinabove, are being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Assistant Commissioner for Patents, Mail Stop AF, P.O. Box 1450, Alexandria, VA 22313-1450, on this 17th day of November, 2003, at 12:45pm (Central Time).

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